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Review Article

Diversified Application of Garlic (*Allium sativum*) Products

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Abstract

The plant is a bulb growing to 25-70 cm with hermaphrodite flowers. Leaves and cloves of A. sativum have been used in traditional medicine of Iran and other countries for a long time. It is pointed out that other sulfur compounds such as diallyl disulphide (DDS), S-allylcysteine (SAC) and diallyl trisulfide (DTS) also have some roles in the effects of the plan. In addition to A. sativum, allicin, ajoene and other organosulfides are present in A. hirtifolium and play important pharmacological roles. Ajoene, another constituent of garlic, is responsible for many pharmacological activities of this plant specially its antifungal effect. This substance is more effective in association with antifungal drugs (sulfametoxazol/ trimethoprim) in the treatment of mice intratracheally infected with Paracoccidioides brasiliensis. High zones of inhibition were noted with ethanol extracts of A. sativum tested against dermatophytes, saprophytes, and Candida species isolated from infected hospitalized patients. Alcoholic extracts also have potential anticryptococcal activity against murine disseminated cryptococcosis. A novel antifungal protein, designated allivin, was isolated from A. sativum with antifungal activity against Botrytis cinerea, Mycosphaerella arachidicola and Physalosporapiricola.

Administration of moderate doses of garlic along with propranolol has beneficial effects with hypertension and myocardial damage. Garlic in moderate doses with added hydrochlorothiazide (HCTZ) possesses synergistic cardioprotective and antihypertensive properties against fructose-and isoproterenol-induced toxicities, by increasing the lactate dehydrogenase, creatinine phosphokinase, and superoxide dismutase and catalase activities in heart homogenate when used concurrently or separately. It was concluded that careful addition of garlic in moderate doses might result in beneficial effect during treatment of hypertension in patients with myocardial stress as garlic causes substantial fall in excretion of potassium when compared to HCTZ alone treatment. Combination of garlic or its bioactive constituent, S-allyl cysteine sulphoxide, and captopril exerted super-additive (synergistic) interaction with respect to fall in blood pressure and ACE inhibition. Another study showed that S-allyl-mercapto-captopril (CPSSA), a conjugate of captopril with allicin, was effective in attenuating systolic and diastolic blood pressures as well as significantly reducing glucose levels. The effects of allicin and enalapril on blood pressure (BP) showed similar effects, both of which reduce BP. Garlic has protective effect against atherosclerosis. Sulfur-containing volatiles from garlic are the principal compounds responsible for such property and the most abundant volatile compound is diallyl disulfide followed by diallyl trisulfide. A pure allicin preparation may affect atherosclerosis not only by acting as an antioxidant, but also by other mechanisms, such as lipoprotein modification and inhibition of LDL uptake and degradation by macrophages. A dosage of 600 mg per day decreases ten-year chance of fatal cardiovascular complications in patients with clinical signs of atherosclerosis, whereas in patients who have no signs of atherosclerosis the complications are decreased with dosage of 300 mg per day. As sited above, suppressed LDL oxidation may be one of the powerful mechanisms accounting for the anti-atherosclerotic properties of garlic. Preparations of garlic used as an adjunct agent in treatment of arterial hypertension because of its hypolipemic and antioxidant properties. Organ system specific activity such as angiotensin converting enzyme-inhibiting action contributes to a cardioprotective and blood pressure lowering effect of garlic.

Keywords: omental infarction; caesarian section; abdominal pain; ct scan, emergency medicine

Introduction

Garlic (*Allium sativum* L. Family Liliaceae) is originally from Asia but it is also cultivated in China, North Africa (Egypt), Europe and Mexico. It is well known in Iran and various parts of this plant have long been used in traditional folk medicines of Iran and some other cultures. It is also used as a spice and food additive (Singh *et al.*, 2009 and Eja *et al.*, 2007). The plant is a bulb growing to 25-70 cm with hermaphrodite flowers (PDR for Herbal Medicines, 2000). Leaves and cloves of A. sativum have been used in traditional medicine of Iran and other countries for a long time (Mikaili and Mehdioghli, 2010 and EL-mahmood, 2009). It is pointed out that other sulfur

compounds such as diallyl disulphide (DDS), S-allylcysteine (SAC) and diallyl trisulfide (DTS)also have some roles in the effects of the plant (Lanzotti *et al*., 2012). In addition to A. sativum, allicin, ajoene and other organosulfides are present in A. hirtifolium and play important pharmacological roles (Azimi *et al*., 2011).

In another study, the aqueous extract exhibited antibacterial activity against gram positive (Bacillus subtilis, Staph. Aureus) and Gram negative (E. coli and Klebsiella pneumoniae) strains, while methanol extract showed antimicrobial activity against all the tested microorganisms except Stap. Aureus (Meriga *et al*., 2012).

Garlic ethanolic extract showed maximum activity against B. subtilis (Pundir et al., 2010). Allitridi, a proprietary garlic derivative, has been successfullyused to treat systemic bacterial infections (such as Helicobacter pylori) in China (Liu *et al*., 2010). It was shown in another study that the extract of garlic strongly inhibits Sal. Enteritidis; however Staph. Aureus showed less sensitivity (Benkeblia, 2004). The significant antibacterial activity of garlic extracts on streptomycin-resistant strains (Gram-positive Staph. aureus and Gram-negative E. coli) solely and in synergism with streptomycin has also been proved (Palaksha *et al*., 2010). In a study by Lai and Roy (2004), fresh extracts of A. sativum (garlic) and Nigella sativum (black cumin) had more antibacterial activity against the isolates of the urinary tract infection, compared to the individual extract or drugs, such as cefalexin, cotrimoxazole, and nalidixic acid (Lai and Roy, 2004). The main compound that is suggested to be responsible for this effect of garlic is volatile allyl methyl sulfide (AMS) as a lead compound of volatile garlic metabolites (Becker *et al*., 2012). Garlic extract was also effective against Streptococcus mutans when tested both in vitro and in vivo. As Strep. mutans is one of the primary aetiological organisms in dental caries development, garlic extract mouth rinse might be used effectively in the prevention of dental caries (Chavan *et al*., 2010).

An in vivo study showed that antibody-alliinase conjugates and alliin are effective against murine pulmonary aspergillosis (Appel *et al*., 2010). Another in vitro study showed both intrinsic antifungal activity of allicin and its synergy with the azoles, in the treatment of candidiasis (Khodavandi *et al*., 2010). Studies on the effect of Amphotericin B (AmB) against C.albicans showed that allicin enhances significantly the effect of AmB against Candida albicans, Saccharomyces cerevisiae and against Aspergillus fumigatus in vitro and in vivo (An *et al*., 2009 and Ogita *et al*., 2006). It was found in another study that polymyxin B (PMB), is effective against various yeasts and filamentous fungi when used in combination with allicin. This combination increases the plasma membrane permeability in Saccharo cerevisiae. Swollen spherical structure of the yeast disappeared as a result of structural alterations of its vacuole caused by the synergistic activity between PMB and allicin combination (Ogita *et al*., 2007). Changes in antioxidant metabolites and antioxidant activity in the presence of DADS were found in C. albicans and C. tropicalis. DADS caused a decrease in the activity of all antioxidant enzymes except catalase (Yousuf *et al*., 2010). One study showed that six different mixtures of garlic distilled oils containing diallyl disulfide (DDS) and diallyl trisulfide (DTS), are active against a number of yeasts (C. albicans, C. tropicalis and Blastoschizomyces capitatus) (Avato et al., 2000). Essential oil vapors from A. sativumalso have inhibitory activity against Ascosphaera apisin in vitro (Kloucek *et al*., 2012). In one study, allicin was shown to be more potent in the growth inhibition of C. albicans and also suppression of HWP1 gene expression in comparison with fluconazole, a commonly used antifungal. This compound does not occur in garlic until it is crushed or injured (Londhe *et al*., 2011). Ajoene, another constituent of garlic, is responsible for many pharmacological activities of this plant specially its antifungal effect (Ledezma *et al*., 2006). This substance is more effective in association with antifungal drugs (sulfametoxazol/ trimethoprim) in the treatment of mice intratracheally infected with Paracoccidioides brasiliensis (Thomaz *et al*., 2008). High zones of inhibition were noted with ethanol extracts of A. sativumtested against dermatophytes, saprophytes, and Candida species isolated from infected hospitalized patients (Shamim *et al*., 2004). Alcoholic extracts also have potential anticryptococcal activity against murine disseminated cryptococcosis (Khan and Katiyar, 2000). A novel antifungal protein, designated allivin, was isolated from A. sativum with antifungal activity against Botrytis cinerea, Mycosphaerella arachidicola and Physalosporapiricola (Wang and Ng, 2001). An ultrastructural study showed that allicin is able to produce morphological changes in the male Schistosoma mansoni (Lima *et al*., 2011). Another study indicated that Allicin has antiparasitic activity against Plasmodium falciparum and Trypanosoma brucei brucei (Waag *et al*., 2010). It was demonstrated that after Alchinal administration, the number of adult forms and muscular larvae of this parasite was significantly decreased (Bany *et al*., 2003). Garlic oil is effective against a wide range of microorganisms including Plasmodium spp, Trypanosoma spp, Leishmania spp, Giardia spp, and Cochlospermum planchonii (Anthony *et al*., 2005). In an in vitro study the ethanol, dichloromethane and water extracts of A. sativum were shown to have anthelmintic activity against Haemonchus contortus from sheep. The ethanol extract was the most effective in decreasing larval count (Ahmed *et al*., 2012). Another study showed that garlic is effective against nematodes. Aqueous extract from garlic has good activity against Trichuris muris and Angiostrongylus cantonensis when followed by chloroform extract (Klimpel *et al*., 2011). In all in vitro tests, the target parasites died. In addition, the same composition was effective against the intestinal fluke Echino caproni, but not against the liver fluke F. hepatica in the final host, while both worms were killed in vitro (Abdel-Ghaffar *et al*., 2011). The extract of A. sativum also possesses mosquito larvicidal properties. It is effective against filarial mosquito Culex quinquefasciatus (after 24 hr treatment) (Singha and Chandra, 2011), Cul. Quinque fasciatus and Anopheles stephensi (Martinez-Velazquez *et al*., 2011). The insecticidal activity of A. sativum against larvae of Aedes albopictus (Skuse *et al*., 2011) (Tedeschi), Lycoriella ingénue (Park *et al*., 2006).

One study showed that Allicin-containing supplements can prevent attacks by the common cold virus (Josling, 2001). In a study investigating the effect of Allitridin (diallyl trisulfide, a compound from A. sativumextraction) on the replication of HCMV and the expression of viral immediate-early genes, it was revealed that this substance has anti-HCMV efficacy (Zhen *et al*., 2006).

A statistical study showed that individuals whose blood pressures are on the lower side are more likely to consume more garlic in their diets (Qidwai *et al*., 2000). Various epidemiologic studies have indicated an inverse correlation between garlic consumption and progression of cardiovascular disease (Rahman and Lowe, 2006). The authors are of the opinion that garlic is effective in treatment of mean systolic blood pressure but not d-penicillamine (Kianoush *et al*., 2012). In one study the aqueous garlic extract (AGE) caused a decrease in blood pressure and bradycardia by direct mechanism not involving the cholinergic pathway, suggesting a likely involvement of peripheral mechanism for hypotension (Nwokocha *et al*., 2011). Another study showed that AGE prevents oxidative stress, systolic blood pressure, aortic NAD (P)H oxidase activity and vascular remodeling in rats with metabolic syndrome (Vazquez-Prieto *et al*., 2010). It has been also shown that preparations of garlic may be tentatively used as an adjunct agent in treatment of arterial hypertension because of its hypolipemic and antioxidant properties (Duda *et al*., 2008). Organ system specific activity such as angiotensin converting enzyme-inhibiting action contributes to a cardioprotective and blood pressure lowering effect of garlic (Sener et al., 2007). The authors are of the opinion that the blood pressure lowering effect of garlic in rats (two-kidney one-clip model) may be partly mediated through the nitric oxide (NO) pathway, by enhanced NO synthesis (Al-Qattan *et al*., 2006). However, harmful effects were observed in the RG group, including a decrease in erythrocytes, an increase in reticulocytes, and generation of

papilloma in the forestomach (Harauma and Moriguchi, 2006). Another study showed that garlic is a potent vasorelaxant and could reduce the atherogenic properties of cholesterol (Zahid Ashraf *et al*., 2005).

A small pilot study indicated the potential ability of aged garlic extract to inhibit the rate of progression of coronary calcification (Budoff *et al*., 2004). In a study garlic appeared to be a good adaptogen to be utilized in patients with coronary artery disease (Verma *et al*., 2005). One study indicated that increased intake of garlic has been associated with reduced mortality in cardiovascular patients or reduced incidence of myocardial infarction, stroke, and hypertension (Yang *et al*., 2011). Another study showed that garlic may beneficially affect two risk factors for atherosclerosis--hyperlipidemia and hypertension (Ali *et al*., 2000).

Authors concluded that the total antioxidant status can be significantly improved by treatment with garlic (Drobiova *et al*., 2011). An ivitro study showed that intravenous administration of garlic extracts produced dose-dependent and reversible hypotensive and bradycardic effects (Brankovic *et al*., 2011). As a result, a number of sulfide-donor drugs, including garlic-derived polysulfides such as diallyl disulfide, diallyl trisulfide and S-ally cysteine, are currently being designed and investigated for the treatment of cardiovascular conditions such as hypertension (GU and Zhu, 2011 and Lavu *et al*., 2011). Garlic-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide which relaxes vascular smooth muscle, induces vasodilation of blood vessels, and significantly reduces blood pressure (Ginter and Simko, 2010). The data suggested that the antihypertensive and renoprotective effects of SAC and AG are associated with their antioxidant properties and that they may be used to ameliorate hypertension and delay the progression of renal damage (Cruz *et al*., 2007). Ithas been shown that time-released tablets of Allicor are more effective in the treatment of mild and arterial hypertension than regular garlic additives (Sobenin et al., 2009). It was shown in a study that administration of garlic extract decreases systolic and diastolic blood pressure only in hypertensive animals with no such effect in normotensive ones (Durak *et al*., 2004). Allyl methyl sulphide (AMS) and diallyl sulphide (DAS), two garlic derivatives, are shown to inhibit migration and angiotensin II-stimulated cell-cycle progression in smooth muscle cells of aorta. As a result, AMS and DAS may serve as effective antioxidant compounds in the arterial structural changes caused by hypertension (Castro et al., 2010). In a study, garlic powder and iloprost inhalation demonstrated clinical improvements in the pre- and in the post-transplant period (Thevenot *et al*., 2009).

Administration of moderate doses of garlic along with propranolol has been shown to have beneficial effects in animals with hypertension and myocardial damage (Asdaq and Inamdar, 2011). Another study indicated that garlic in moderate doses with added hydrochlorothiazide (HCTZ) possesses synergistic cardioprotective and antihypertensive properties against fructose- and isoproterenol-induced toxicities, by increasing the lactate dehydrogenase, creatinine phosphokinase, superoxide dismutase and catalase activities in heart homogenate when used concurrently or separately (Asdaq and Inamdar, 2011). It was concluded that careful addition of garlic in moderate doses might result in beneficial effect during treatment of hypertension in patients with myocardial stress as garlic causes substantial fall in excretion of potassium when compared to HCTZ alone treatment in rats (Asdaq and Inamdar, 2009). One study represented that combination of garlic or its bioactive constituent, S-allyl cysteine sulphoxide, and captopril exerted super-additive (synergistic) interaction with respect to fall in blood pressure and ACE inhibition (Asdaq and Inamdar, 2010). Another study showed that S-allyl-mercapto-captopril (CPSSA), a conjugate of captopril with allicin, was effective in attenuating systolic and diastolic blood pressures as well as significantly reducing glucose levels (Younis *et al*., 2010). A comparable study between the effects of allicin and enalapril on blood pressure (BP) showed similar effects, both of which reduce BP (Elkayam *et al*., 2001). Also, numerous animal studies have reported that garlic can have protective effect against atherosclerosis (Espirito Santo *et al*., 2004). Sulfur-containing volatiles from garlic are the principal compounds responsible for such property and the most abundant volatile compound is diallyl disulfide followed by diallyl trisulfide (Calvo-Gómez *et al*., 2004). A pure allicin preparation may affectatherosclerosis not only by acting as an antioxidant, but also by other mechanisms, such as lipoprotein modification and inhibition of LDL uptake and degradation by macrophages (Gonen et al., 2005). A dosage of 600 mg per day decreases ten-year chance of fatal cardiovascular complications in patients with clinical signs of atherosclerosis, whereas in patientswho have no signs of atherosclerosis the complications are decreased with dosage of 300 mg per day (Gromnatskiĭ *et al*., 2007). As sited above, suppressed LDL oxidation may be one of the powerful mechanisms accounting for the anti-atherosclerotic properties of garlic (Lau, 2001). Other possible mechanisms for lipid lowering and anti-atherogenic effects of garlic include inhibition of the hepatic activities of lipogenic and cholesterogenic enzymes that are thought to be the origin for dyslipidemias, increased excretion of cholesterol and suppression of LDL-oxidation (Mathew and Biju, 2008). In an in vitro study, the potential anti-atherosclerotic property of moderate and high doses of garlic homogenate (GH was significantly attenuated by propranolol and hydrochlorothiazide. However, GH anti-hyperlipidemic activity was augmented by captopril (Asdaq *et al*., 2009). This finding suggests that EGP might be useful in the prevention of atherosclerosis (Yamaji *et al*., 2004) monstrated significant antithrombotic actions both in vitro and in vivo. A study suggested that odorless garlic not only activates fibrinolytic action by accelerating (tissue-type plasminogen activator) t-PA-mediated plasminogen activation, but also suppresses the coagulation system by down regulating thrombin formation, suggesting a beneficial role in preventing pathological thrombus formation in such cardiovascular disorders (Fukao *et al*., 2007).

Another survey indicated that garlic extracts act through inhibition of the ADP (adenosine diphosphate) pathway. Their mechanisms of action are comparable to that of the clinically used drug clopidogrel. The pharmacologically active component of the extracts appears to be lipophilic rather than hydrophilic (Hiyasat *et al*., 2009). One study mentioned that the aromatic thiosulfonate derived from garlic is a very effective inhibitor of platelet aggregation (MacDonald et al., 2004). Diallyl trisulfide (DATS) is one of the major constituents in garlic oil and has demonstrated various pharmacological activities, such as antithrombotic (Choi and Park, 2012). Supplementation of garlic oil at 5 mg/kg BW had anticoagulation effect in this study (Chan *et al*., 2007).The antiplatelet activity of methyl allyltrisulfide (MATS), a component commonly present in steam-distilled garlic oil, has also been demonstrated. MATS inhibits arachidonic acid cascade at the reaction site with PGH synthase (Ariga et al., 2000). It was also shown that the loss of activity, and the partial loss of antithrombotic effect in crushed-cooked garlic may be compensated by increasing the amount consumed (Cavagnaro *et al*., 2007). Authors mentioned that sulfur compounds' contribution to the health promotion in allium species are produced via enzymic and thermal reactions. Potent antithrombotic agents which have been identified as allyl trisulfides, dithiins, and ajoene in garlic are thermochemically transformed forms of allicin (allyl 2-propenethiosulfinate) (Nishimura *et al*., 2000). A study showed that allicin had the strongest antiplatelet activity at 0.4 mM inhibiting aggregation by 89% (Briggs *et al*., 2000). Ajoene is another potent antiplatelet compound isolated from alcoholic extracts of garlic. It is suggested that ajoene may be potentially useful for the acute prevention of thrombus formation induced by severe vascular damage, mainly in arterial sites with low local shear rates (Mousa, 2010). It has been suggested that supplements of garlic could adversely affect coagulation when taken alone or in combination with antiplatelet medications (Stanger *et al*., 2012). In a study coadministration of aged garlic extract and cilostazol did not enhance the antiplatelet activity compared with individual drugs (Mateen *et al*., 2011). Another study suggested that aged garlic extract is relatively safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin oral

anticoagulation therapy (Macan *et al*., 2006). However, alterations in drug use may be required for those patients undergoing invasive surgical procedures. It is recommended that herbal supplements, such as garlic, must be discontinued 2 weeks prior to receiving invasive surgical procedures (Spolarich and Andrews, 2007). One survey mentioned that garlic has antihyperlipidemic, hypocholesterolaemic and hypotriacylglyceride activities (Kuda et al., 2004). Thus, dietary garlic was effective in reducing the oxidant stress, which was indicated by an increase of antioxidant activity and a decrease of lipids in the rats' blood (Gorinstein *et al*., 2006). In another study, garlic powder significantly ($P < 0.05$) lowered the animal`s blood lipid levels (Kuo *et al*., 2008). Garlic has been shown to have applications as a hypoglycemic agent (Sengupta *et al*., 2004). A study suggested a new mechanism for the hypolipidemic effect of fresh garlic. Long-term dietary supplementation of fresh garlic may exert a lipid-lowering effect partly through reducing intestinal MTP (microsomal triglyceride transfer protein) gene expression, thus suppressing the assembly and secretion of chylomicrons from intestine to the blood circulation (Lin *et al*., 2002). Short-term garlic therapy in adults with mild to moderate hypercholesterolemia does not affect lipid levels (Peleg *et al*., 2003).

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